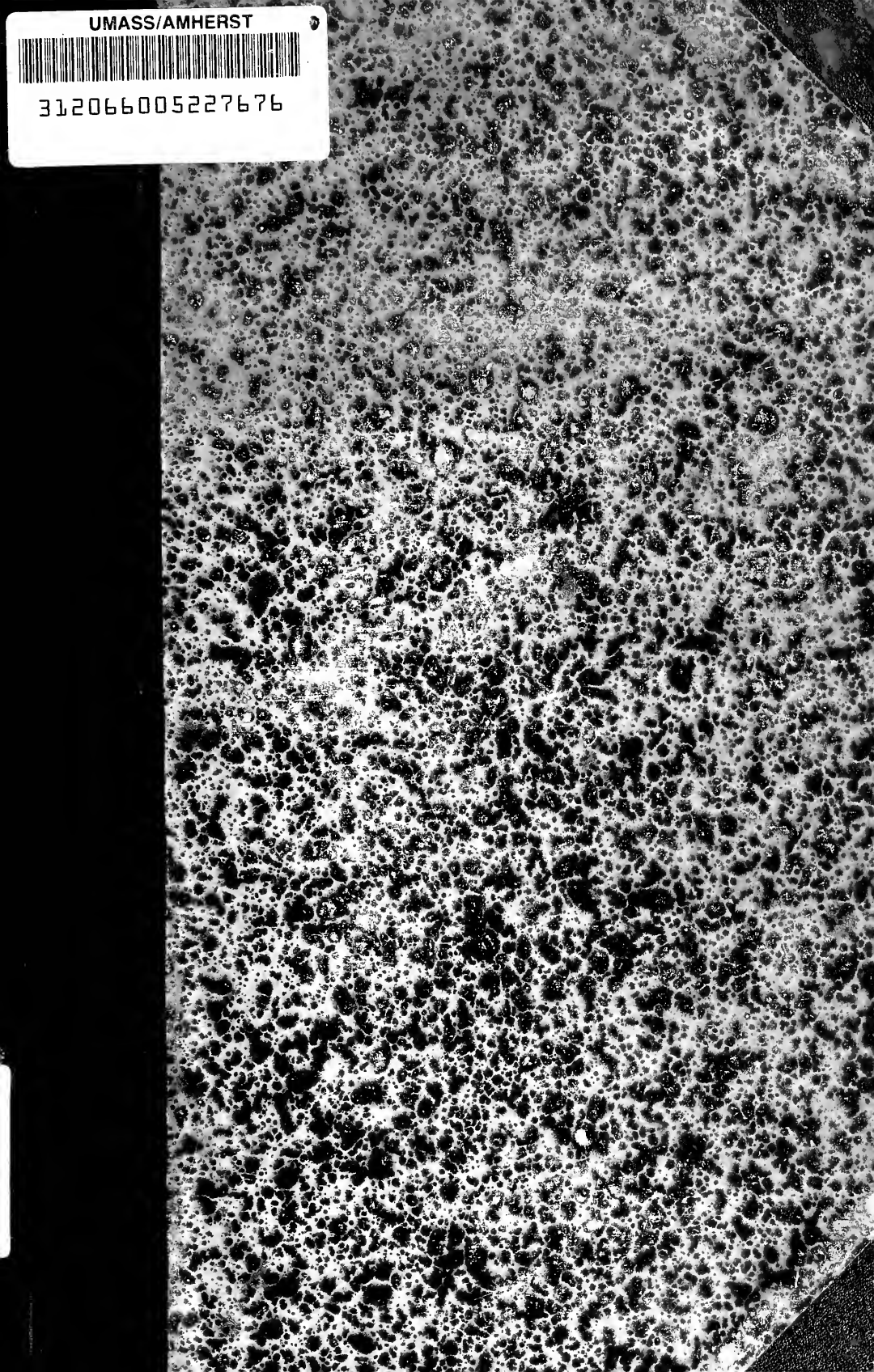

A STUDY OF

EXPERIMENTAL PNEUMONITIS IN THE RABBIT

INDUCED BY THE INTRATRACHEAL INJECTION OF DEAD TUBERCLE BACILLI

BY

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EXPERIMENTAL PNEUMONITIS IN THE RABBIT,

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Introduction.

A great deal of the morphological complexity of the lesions of the lungs in both acute and chronic tuberculosis is due to inflammatory processes which do not present the characteristic features of tubercular inflammation. When we have taken account of the miliary tubercles, both single and conglomerated, of the larger and smaller masses of epithelioid-cell growth which we call diffuse tubercle tissue, and of the various aggregates of these—often in a condition of more or less advanced coagulation necrosis; when we have further brought into line that series of more or less exteusive inflammatory consolidation of the lungs in which, without the development of characteristic tubercle tissue, coagulation necrosis and often disintegration of both lung and exudate occur, under the influence of the living growing tubercle bacillus—there still remains a series of intra-alveolar inflammatory exudations about and among the more characteristic tubercular areas whose cause and origin are not sufficiently understood. These exudations are sometimes fibrinous, sometimes epithelioid in character; sometimes they are largely composed of small spheroidal cells;, or, which is more frequently the case, all three forms of exudate are intermingled.

No doubt a double infection sometimes occurs, so that associated with the lesions directly induced by the tubercle

bacillus are those brought about by the pneumococcus or the pyogenic bacteria, or by other occasional inciters of suppurative inflammation. But this appears to be of comparatively infrequent occurrence.

On the other hand, there is not infrequently in tuberculosis a considerable formation of new connective tissue in the lungs, either circumscribed or diffuse, the relationship of which to the specific tubercular lesion is not very clear.

It was with a view of learning, if possible, to what extent dead tubercle bacilli may be capable of inducing these and other phases of complicating non-specific forms of inflammation of the lungs that the studies were undertaken which are now to be recorded.

Experiments.

In a paper recently published by Dr. Hodenpyl and myself * it was shown that dead tubercle bacilli, introduced in moderate numbers into the ear vein of the rabbit, are capable of inducing after a time at their seat of lodgment in the blood-vessels, especially of the lungs and liver, circumscribed growths of new cells which in many respects closely resemble miliary tubercles. These new growths differ, however, fundamentally from genuine miliary tubercles in that they do not, so far as we could observe, undergo cheesy degeneration and never contain live tubercle bacilli, and are hence not infectious. Hand in hand with the development of these new tissue structures there occurs, under the influence of the dead tubercle bacillus, a proliferation of endothelium and an extravasation of leucocytes. It was shown, in other words, that *dead tubercle bacilli possess not only positive chemotactic powers, but are, in a marked and peculiar way, capable of stimulating various phases of cell proliferation.* But, in order to produce these tubercle-like structures in the simple uncomplicated forms described in our paper above referred to, it is necessary, so far as our observations go, to introduce the dead bacilli well distributed in very minute particles through the fluid used for injection, because in this way one avoids any considerable immediate vascular disturbance at the seat of lodgment of the dead germs.

* *N. Y. Medical Journal*, June 6 and 20, 1891.

If, on the other hand, we inject into the ear vein of the rabbit an emulsion of dead tubercle bacilli in which the flocculi formed of the bacillary masses are large, so that they block up the smaller blood-vessels where they lodge, one gets an entirely different series of results. This is especially marked in the lungs, to which organs our attention in this paper is largely limited. It will be remembered that in our former experiments the characteristic lesions were slow in developing, from two to six weeks often elapsing before any gross lesions were produced, while in some cases no gross but only microscopical changes appeared. The animals did not, as a rule, experience any ill effects from their dosage.

But when larger flocculi of dead bacilli are injected in considerable quantity, a certain proportion of the animals die at once from cerebral embolism. Others fall directly into convulsions, apparently from the same cause, but speedily recover. The larger proportion, however, do not appear to suffer from the immediate effects of the injection, if this be made slowly. If, now, the animals which have survived the injection of these larger masses of bacilli be killed at intervals of from forty-eight hours to ten days, or if they die during this period, it will be found in a considerable proportion of cases that even as soon as the second day after the injection the lungs are more or less thickly beset with small, white, rounded, or branching masses of solidified lung tissue.

Microscopical examinations of these solid areas show that they consist of one or more much-dilated small blood-vessels surrounded by an irregular zone of air spaces, both of which are densely packed with small spheroidal cells resembling leucocytes. In sections stained for tubercle bacilli it will be seen that within the blood-vessels, intermingled with the leucocytes and blood-plates which form the bulk of the thrombi, are large scattered masses of tubercle bacilli. But the bacilli are not confined to the vessels. Everywhere in the air-vesicles of the consolidated areas they lie scattered among the cells which fill the air-spaces or are clustered within them. The whole picture conveys the impression that, either owing to the disturbance of the circulation by the occluding bacterial embolus or to the irritating

effects of the dead germs themselves, there has been not only a dense gathering of leucocytes in the vessels, forming voluminous thrombi, but that hand in hand with the emigration of leucocytes from the affected vessels there has been a diapedesis of dead tubercle bacilli. Whatever may be the reason, the fact is that within forty-eight hours the tubercle bacilli in large numbers have got outside the blood-vessels where they first lodged and are mingled with the exudation in the contiguous air-vesicles. While this great collection of leucocytes in the blood-vessels and in their adjacent air-vesicles may be in part due to the simple embolic vascular disturbance, it would seem to me that it may be largely owing to the marked chemotactic powers which the dead tubercle bacilli possess, as has been shown by several observers.

I have not followed this special line of observation beyond a series of injections on fourteen rabbits, because the point which I had in view can be more directly reached by a form of experiment which eliminates the extensive and often profound vascular changes thus brought about.

What I wished to ascertain in these studies was the effects of dead tubercle bacilli introduced directly into the air-vesicles of the lung of the rabbit in considerable quantity through the trachea. To record these results is the primary purpose of this paper.

The material used for the intratracheal injections was prepared as follows: A voluminous flask culture of the tubercle bacilli in glycerin bouillon, two months old, was filtered through sterilized filter paper to separate the bacterial mass. The latter was now carefully washed in the filter with large quantities of sterilized water, and then with about a hundred times its volume of distilled water was steamed in a small flask for two hours in the Arnold sterilizer. The fluid was now filtered off—to remove any of the metabolic products of the life process of the bacillus which might be soluble under these conditions—and again thoroughly washed in the filter. The bacterial mass, while still moist, was now again mixed with about one hundred times its volume of water and again boiled for two hours, when it was ready for use.

I have, in another set of experiments, boiled the cult-

ures in fifty per cent. of glycerin for an equal time, filtering off and washing in the same way.

In another set of experiments I have used glycerin agar cultures of the tubercle bacillus, sterilized and washed in the same way.

While these three sets of animal experiments were performed separately and at different times, the results were identical, so that we may consider them as forming one series.

It was now assumed that this milky emulsion, whichever way prepared, contained no living tubercle bacilli, and that all the poisonous materials which might have been present in the fluids of the original culture or clinging to the surfaces of the dead bacilli had been removed from the material, at least in so far as they are soluble in boiling water or in glycerin and water.

The mode of operative procedure was as follows: After cutting away the hair and sterilizing the skin about the neck of the rabbit, a small incision was made, exposing the trachea, and the needle of the injecting syringe was thrust through its wall. About two cubic centimetres of a milky emulsion of dead tubercle bacilli was slowly introduced in this way, the animals being held upright and turned about from side to side during and for a few moments after the injection, so that the fluid might run well down into various parts of the lungs. The animals bear this injection perfectly well, often experiencing a momentary dyspnœa, and the wounds of the neck always closed promptly.

Thirty-four animals were operated upon in this way and were killed at the following intervals: Two on the first day after the operation, three on the second day, one on the fourth, one on the fifth, two on the sixth, one on the eighth, one on the eleventh, one on the thirteenth, one on the seventeenth, one on the eighteenth, two on the twentieth, three on the twenty-first, two on the twenty-third, one on the twenty-fourth, two on the twenty-seventh, two on the twenty-ninth, two on the thirty-first, one on the thirty-fourth, three on the forty-first, one on the fifty-third, and one on the seventy-second.

The results of the introduction of dead tubercle bacilli into the lungs of rabbits through the trachea in this way

are so certain, so positive, and so uniform, that it seems to me wiser to give the general effects of the action of the dead germs than the story of particular animals.

The gross appearance of the lungs of animals operated upon in this way changes considerably from day to day, and the general topography of the lesions varies greatly with the vicissitudes of the experiment, in accordance with which the masses of bacilli may be abundant or scanty, large or small, are grouped in one lung or part of a lung, or are widely disseminated through both organs. Thus, one or both lungs may be irregularly besprinkled with small miliary or submiliary areas of consolidation, or such areas may be associated with larger areas of diffuse consolidation which may occupy portions of a lobe, or a whole lobe, or nearly a whole lung. The situation of the lesion is directly dependent upon the seat of lodgment of the dead bacilli, while its extent appears to be directly and uniformly dependent upon the amount of bacilli introduced or the length of time allowed to elapse between the injection and the killing of the animals. No lesions, either gross or microscopical, were found in any of the viscera except the lungs.

The general course of events after the introduction of dead tubercle bacilli into the lungs of rabbits under the conditions set forth above is as follows :

As early as twenty-four hours, if the animal is killed, extensive lesions are developed. The lungs are moderately congested, and numerous white spots of consolidation, from 0·5 to 2 millimetres in diameter, are seen shimmering through the pleura. The cut surface of the lungs, as a rule, reveals more extensive lesion than would be expected from the superficial inspection of the organs. The cut surfaces usually show large numbers of irregularly branching or isolated and scattered white, dense, airless areas, commonly most abundant posteriorly, which correspond with the bronchi and groups of their adjacent air-spaces. There is usually special congestion of the blood-vessels immediately about these consolidated areas in some parts of the lungs.

The gross appearance of the cut surface of a lung twenty-four hours after the injection is indicated by Fig. 1.

The microscopical examination shows that the white

areas of consolidation are due to an extreme filling and distention of the smaller bronchi and portions of their contiguous air-spaces with densely packed masses of small spheroidal cells resembling leucocytes. Many of the smaller blood-vessels in these consolidated areas are packed with small spheroidal cells. In some places there is a very slight increase in the number of the epithelial cells of the air-vesicles.

Sections stained for tubercle bacilli show that wherever this gathering of small spheroidal cells had occurred there are tubercle bacilli, usually in very large numbers. Indeed, tubercle bacilli are nowhere found in the air-spaces in any considerable numbers without being closely intermingled with these small cells.

While the medium and smaller bronchi in the consolidated areas are closely packed with the small spheroidal cells and dead tubercle bacilli, the epithelial lining of the bronchi is almost wholly intact. There are neither inflammatory nor degenerative nor exfoliative changes in the bronchial epithelium. It appears more as if the small cells had been forced up into the bronchi from the groups of communicating air-spaces which are so densely packed with them. In some places, especially where the accumulation of small spheroidal cells in the air-spaces is large and the dead bacilli are numerous, the cell bodies appear homogeneous and their outlines indistinct; but their nuclei are, as a rule, well stained, so that the dense masses of exudate present somewhat the appearance of coagulation necrosis, but are still evidently not in this condition.

The result, then, of the action of dead tubercle bacilli in large numbers in the air-spaces of the rabbit's lung for twenty-four hours is, in general, the accumulation in enormous numbers about the bacilli, and nowhere else, of small spheroidal cells resembling leucocytes.

The microscopical appearance of a small bronchus showing bacilli is given in Fig. 2, and of two adjacent air-vesicles in Fig. 3.

At the end of the second day the gross appearance of the lungs differs little from that at the end of the first. Microscopical examination shows that the small bronchi and air-spaces in groups are densely packed and distended with

small spheroidal cells, many of which, especially where there are many tubercle bacilli, have undergone a peculiar change. The nuclei remain apparently unaltered, but the bodies are swollen, no longer granular, but nearly homogeneous and glassy in appearance, and in places have run together, forming shining masses. This change in the accumulated cells may begin, as already indicated, and may even be fairly well marked within twenty-four hours after the injection.

The empty air-spaces close to those which are thus filled with small cells and dead tubercle bacilli are so squeezed that their lumina are for the most part closed. They then form an ill-defined, irregular, solid zone of atelectasis immediately about and in places running into the exudative area.

In animals killed from the fourth to the sixth day after the injection into the trachea the gross appearance of the lungs is essentially similar to that presented at the end of the first, save that around the white consolidated areas there are usually visible narrow, irregular, grayish, translucent zones of consolidation.

The smaller bronchi, in places, and their groups of related air-spaces, are filled, as at an earlier period, with dense masses of intermingled small spheroidal cells and dead but readily stained tubercle bacilli. Where these central masses are dense and harbor many bacilli, the cells are, as at an earlier period, homogeneous and diffusely outlined. The blood-vessels in and near these consolidated areas are often crowded with small spheroidal cells, and around many of the larger vessels of these areas there is a perivascular sheath of spheroidal cells.

The translucent consolidated borders of these areas are largely formed by the filling of the surrounding air-spaces with collections of epithelioid cells, or giant cells, or small spheroidal cells, or all of these variously intermingled. There is much variability in the number of giant cells in the new tissue, which I can only account for by individual peculiarity of the animals. In an animal killed on the fourth day, for example, there was almost no tendency to produce giant cells, while on the fifth day an animal treated similarly showed them in enormous numbers.

Tubercle bacilli are present in this border zone, but

in less numbers than in the primary areas of consolidation.

Fig. 4 shows the edge of one of these areas of consolidation from the lung of a rabbit killed four days after the tracheal injection of the dead tubercle bacilli.

The essential change, then, which takes place in the lesion toward the end of the first week is the formation and accumulation of cells—epithelioid and giant—in the air-spaces about the primary focus of small-cell collection, and the infiltration and thickening of the walls of the involved air-spaces.

In the second week two distinct sets of changes occur in the consolidated areas, whether these be large or small:

First, there is a well-marked tendency to disintegration and absorption in the central portion of the solid areas—that is, in that portion first to appear at the seat of lodgment of the bacilli, and which is formed of densely packed masses of small spheroidal cells mingled with large numbers of dead bacilli. The walls of the old air-spaces in this area are apparently dead, so that the central portion of the solid areas is made up of a mass of necrotic, disintegrating tissue, which appears to be growing smaller by absorption.

The *second* set of changes is in the translucent peripheral zone which now forms the most prominent feature of the consolidated area. This peripheral translucent zone is formed of air-spaces more or less closely packed with epithelioid cells and giant cells, the former largely preponderating and showing in the most exquisite way the varied nuclear figures of indirect cell division. The walls of the air spaces of this peripheral zone are thickened, apparently from the accumulation of fluid and small spheroidal cells within them, and their blood-vessels are in places widely distended with leucocytes, so that the areas of consolidation are often distinctly bordered by a rim of small spheroidal cells.

In the immediate vicinity of clusters of the dead tubercle bacilli the formation of epithelioid cells is not so regular and perfect as at a little distance from them, or where they are more sparsely scattered.

Near the clusters of bacilli the new cells are massed in

the form of ill-defined giant cells, or the bacteria are surrounded by an irregular granular or translucent material, into which, here and there, leucocytes have penetrated. One not infrequently sees that the epithelioid cells which have developed around a clump of dead bacilli in an air-space are radially placed around it with their nuclei uniformly crowded to the distal portion of the cell.

The result of these minute alterations is that to the naked eye the solid areas at this time present the appearance of gray, translucent, irregular masses of new tissue, having proportionately small and inconspicuous white centers. The general appearance of the solid areas toward the end of the second week is represented, somewhat schematically, in Fig. 5.

In the third week there is a steady disappearance of the necrotic central portion of the solidified areas, while in the peripheral translucent zone the old air-spaces are steadily obliterated by the thickening of their walls and the disappearance of lines of demarkation between these and the cell-filled air-spaces. So that the original air-spaces come to be represented by larger and smaller collections of closely packed epithelioid cells lying in the meshes of a very vascular and very cellular new connective tissue. The blood-vessels in the new connective tissue have lost all the topographical characters of the original blood-vessels of the affected region, but may be, in part, some of these which have persisted. On the other hand, many of them are certainly newly formed, since one can find in these sections the various phases of blood-vessel development, such as are seen in typical granulation tissue. The appearance of a typical portion of this peripheral zone at about the middle of the third week is shown in Fig. 6.

From the third week on the story is usually one of the steady disappearance of the necrotic center and the conversion of the peripheral areas of consolidation into masses of connective tissue with their continuous decrease in size. The tubercle bacilli, too, become steadily less abundant. This new connective tissue is at first very cellular, as shown in Fig. 7, but the intercellular substance continually increases in amount.

In many of the nodules of new connective tissue por-

tions of the old air-spaces are inclosed by the new tissue and wholly separated from surrounding air-spaces or connected with them by flattened strings of epithelioid cells. These inclosed air-spaces are, as a rule, lined with a continuous layer of cuboidal or flattened cells. There has obviously been a reversion of the epithelial cells lining the inclosed and isolated air-spaces to the embryonal type, as there is under somewhat similar conditions in some phases of chronic phthisis. Fig. 8 shows a typical portion of one of these connective-tissue nodules at this time.

At last nothing is left of the consolidated areas but larger or smaller masses of cicatricial tissue which may or may not harbor a few still stainable granular tubercle bacilli. The time which is required for the conversion of the nodules produced in the lungs by the injection of dead tubercle bacilli into dense cicatrices varies considerably, depending upon the amount of lung tissue involved—that is, upon the size of the primary mass. The smaller ones may disappear to the naked eye inspection as early as the end of the third week; the larger may remain for many weeks. When whole lobes are involved, many weeks may elapse before the conversion of the involved portion into cicatricial tissue. But, in general, the description which I have given above expresses as closely as is possible, with the material at my disposal, the course of events. Sometimes there appears to be little tendency in many of the small nodules to the formation of connective tissue, but the nodules consist, after the lapse of many weeks, of a congeries of air-vesicles greatly diminished in size by the thickening of their walls and densely packed with epithelioid cells and giant cells. In one animal killed on the twenty-third day extensive calcification of one of the connective-tissu nodules had occurred.

I could not observe that the size or nutritive condition of the animals made any difference in the rate of progress of the changes in the lesions. As has been already stated, the lesions in the lungs, even when a large part of a lobe was involved, did not appear to exert any harmful influence on the health and bearing of the animals.

Summary.—These studies show that when dead tubercle bacilli are introduced in small flocculi into the air-

spaces of the rabbit's lung there occurs at their seat of lodgment, first, a large accumulation of small spheroidal cells in the air-spaces. This is immediately followed by a proliferation of epithelioid cells and formation of giant cells in the contiguous air-spaces. Then occur gradual necrosis, disintegration, and absorption of the primary small-celled center and a conversion of the peripheral zone into very cellular and vascular new connective tissue. Hand in hand with the absorption of the necrotic center the new-formed connective tissue becomes denser and less abundant, until finally the seat of lesion is indicated only by a shred or patch of dense connective tissue, which, if the original lesion was not extensive, may be wholly invisible to the naked eye. Sometimes, however, but little connective tissue is formed except in the walls of the involved air-spaces, but the nodules persist for long periods as a congeries of densely packed epithelioid and giant-cell masses.

Remarks.—This is a simple biological study, showing the reaction of certain cells in the rabbit's lungs in the presence of the dead bodies of a well-defined and important species of pathogenic bacteria. It has no necessary bearing on human tuberculosis, nor even on tubercular inflammation in rabbits. And yet when we consider the close analogy between tuberculosis in man and in the rabbit, and the similarity between certain phases of the lesions produced in the rabbit by the living and the dead germs, we are, it seems to me, justified in certain limited conjectures as to the possible or probable bearings of such a study on our conception of human pulmonary tuberculosis.

We may, I think, assume that of all the tubercle bacilli which are present in the body at a given time in any form of tuberculosis, only a certain proportion are alive. This we may fairly assume from what we know of the life history of the tubercle bacillus under artificial cultivation, together with what we know of the life history of bacteria in general, both within and without the body. New individuals form and old ones die with varying degrees of rapidity so long as the environment favors vegetative activity. With the formation of spores and the maintenance of the life of the species in this way when vegetative activity ceases, we have here nothing to do.

It has been abundantly shown in this study and in those on the same theme which have preceded it that the power of taking and retaining the characteristic stain may be retained by the tubercle bacillus long after life in the germ has ceased and after its subjection to prolonged boiling and to the influence of living body cells. It has been shown, too, that dead tubercle bacilli slowly disintegrate and finally disappear when surrounded by living body cells and by the body juices.

The primary difference between the action of the dead and that of the living tubercle bacillus in the rabbit appears to be that the living bacillus proliferates in the body and produces progressive lesions with a marked and characteristic tendency to generalization and to coagulation necrosis—developing an acute infectious disease; while the dead bacillus produces lesions closely similar morphologically in many respects, and yet which are not indefinitely progressive and do not tend to generalization or to the production of an advancing coagulation necrosis, and, furthermore, do not induce an acute infectious disease. The necrosis which develops under the influence of the dead germs differs from that of genuine tuberculosis, not only in its morphological characters, but also in the time of its occurrence. It is one of the earliest of the changes following the primary gathering of cells about the dead bacilli and attains at once its maximum development. The cheesy degeneration of genuine tuberculosis, on the other hand, is a gradually developed and progressive process, and represents the usual culmination of the lesion.

We now know that dead tubercle bacilli can induce in the living body the development of cell structures which, within the limits above indicated, are morphologically characteristic of the lesions of tubercular inflammation. We do not know whether the living tubercle bacilli are capable of stimulating the body cells to the development of such lesions or not, because presumably both the living and the dead germs are present in the ordinary tubercular foci. We must admit the possibility that in acute and in chronic phthisis a certain proportion of the inflammatory foci in the lungs —certain of the broncho-pneumonic areas—may be caused by

dead tubercle bacilli transported from cavities to other parts of the lungs.

The conjecture was expressed in a previous paper on the effects of dead tubercle bacilli by Dr. Hodenpyl and the writer, that the stimulus to cell proliferation in tubercular inflammation might be due to the bacterio-protein of the tubercle bacilli set free during their disintegration. That conjecture this study would seem to sustain.

Whether the characteristic cheesy degeneration of tubercular inflammation is due to an eliminated metabolic product of the living growing germ or to some product or influence as yet wholly unknown, remains to be found out. Experimental studies in that direction are in progress in this laboratory. Studies on the effects of combining the two factors—the dead germ and the metabolic products—by a separate administration in the same animal are also under way, but are not yet sufficiently advanced to permit of definite conclusions.

In view of what we know of the importance of the mustering of various forms of cells in the neighborhood of bacterial invaders of the body as a direct or indirect protection against their ravages, this power of dead tubercle bacilli to stimulate the reproduction of cells becomes of a great deal of apparent significance.

I have alluded, in the papers on this subject above referred to, to the possibility that the development of tubercle tissue in the body may be a conservative action of great importance. The studies here recorded would widen the scope of that conjecture by suggesting the possibility that not only the specific tubercle tissue itself, but the other cell accumulations which in the lungs so often accompany it, may serve an analogous purpose; for we should not forget that whatever shall be the ultimate outcome of researches on the absolute or relative importance of phagocytosis and the germicidal power of the body fluids, the efficiency of the latter is ultimately dependent upon cell activity, as Buchner and others have repeatedly insisted.

In view of this condition of affairs, it is perfectly possible, as Buchner * suggested very soon after Koch's first announcement of the powers of tuberculin, that that substance

* Buchner. *Münchener med. Wochenschrift*, 1890, No. 47.

may owe some of its virtues, if such it possesses, to proteins which have resulted from the degeneration in the cultures of the bodies of the tubercle bacilli.

It is evident from this study that certain of the non-characteristic complicating lesions of the lungs in acute and chronic phthisis referred to at the commencement of this paper, leucocytic and epithelial cell collections in the air-spaces of the lungs, as well as the development of new interstitial connective tissue, may be caused by the presence of dead tubercle bacilli at the seat of lesion.

We have in this form of experimentation on the rabbit a means of study of pulmonary inflammation wholly within our control and most useful for the examination and demonstration of those forms of cell activity which are involved in indirect division.

Finally, the power of inducing at will, without seriously compromising the health of the animal, small circumscribed foci of inflammation of varying intensity, which have a definite history and outcome, may be of no inconsiderable importance in the study of the action of drugs along the lines suggested by Koch's announcement of the localized effects of tuberculin in the body under conditions of focal inflammation analogous with those here experimentally induced.

Our knowledge of the effects of the tubercle bacillus in the body is now, I think, sufficiently advanced for us to make at least a conjectural analysis of its action.

1. So far as the primary morphological lesion is concerned, we may conjecture that the cell growth which is characteristic of miliary tubercle and diffuse tubercle tissue may be due to the action of the protein of the bodies of the germs set free as they degenerate in contact with living cells; and that this production of new tissue may not be intrinsically of such practical significance as has been hitherto supposed; or, if significant, it may be so as a conservative and not as a harmful process.

2. It would seem from our experiments that the cheesy degeneration which is so constant an accompaniment of tubercular lesions may be due to some metabolic product of the growth of the tubercle bacillus wholly distinct from the cell-stimulating bacterio-protein.

3. There still remains the possibility, most evident on clinical grounds, that beyond the factor which causes the tissue cells to grow, and beyond the factor which induces necrosis, there may be yet a third agency of toxic nature to which many of the graver systemic effects of tubercular infection are due.

This mere suggestion of an analysis of the action of the tubercle bacillus in the body is made in conclusion here only in a tentative way, with a view of affording a perhaps only temporary guiding thought in our future study of this most important disease and our future attempts to stay its ravages.

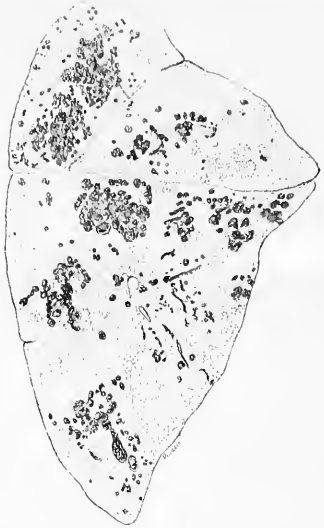

FIG. 1.—Section of lung of rabbit, twenty-four hours after intratracheal injection of dead tubercle bacilli, showing areas of small-cell collection. About twice the natural size.

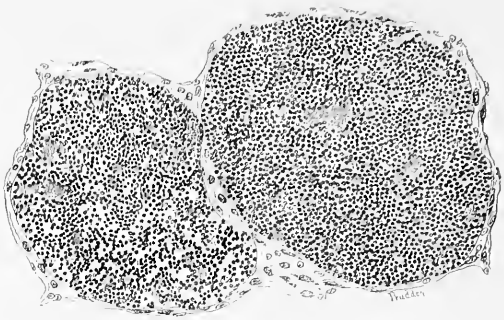

FIG. 3.—Air-vesicles near small bronchus shown in Fig. 2, similarly filled.

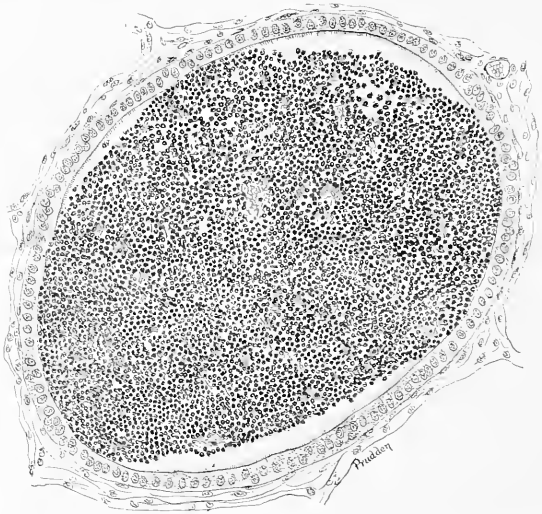

FIG. 2.—Small bronchus of rabbit's lung, twenty-four hours after intratracheal injection of dead tubercle bacilli, showing accumulation of small cells and bacilli.

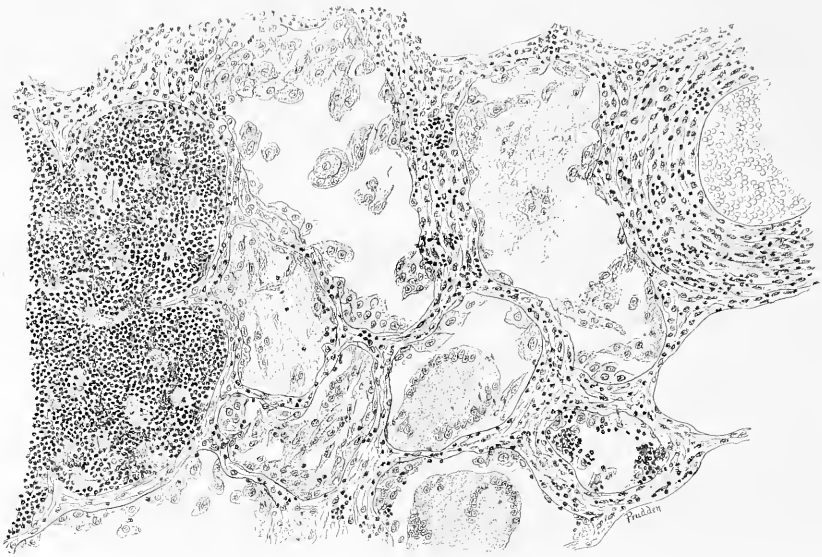

FIG. 4.—Edge of one of the areas of consolidation in the rabbit's lung, four days after intratracheal injection of dead tubercle bacilli. At the left is seen the primary focus of exudation containing small cells, many dead bacilli, and necrotic exudate.

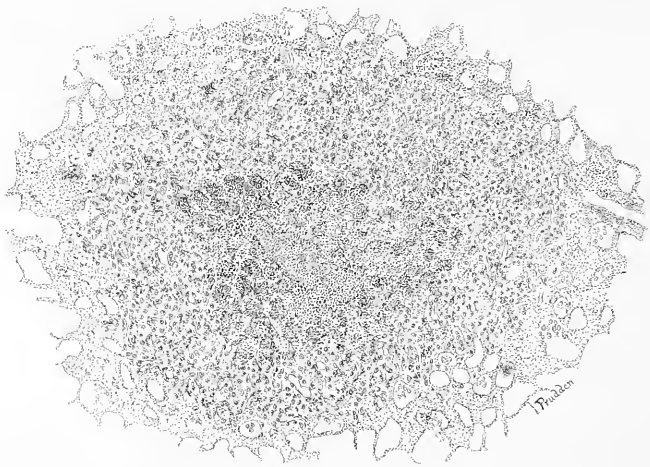

FIG. 5.—Typical nodule in the rabbit's lung on the eleventh day after intratracheal injection of dead tubercle bacilli.

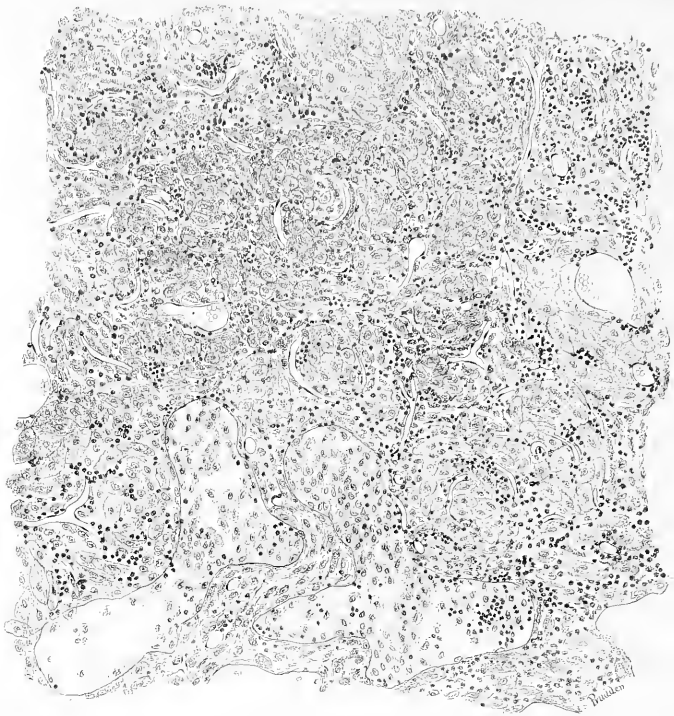

FIG. 6.—Peripheral portion of consolidated area in the rabbit's lung, seventeen days after intratracheal injection of dead tubercle bacilli. A few bacilli are yet demonstrable in the new tissue, but are not shown in the cut.

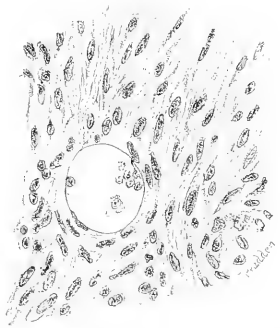

FIG. 7.—Young cellular connective tissue in an area of consolidation in the rabbit's lung, twenty-four days after the intratracheal injection of dead tubercle bacilli.

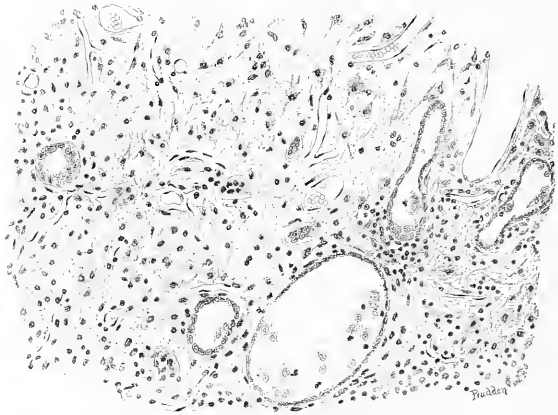

FIG. 8.—Portion of connective-tissue nodule in rabbit's lung, showing the result of the healing process, twenty-nine days after the intratracheal injection of dead tubercle bacilli. The larger openings in the cut are inclosed air-spaces whose epithelial lining has undergone reversion to the fœtal type.